

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 October 2001 (18.10.2001)

PCT

(10) International Publication Number
WO 01/76845 A1

(51) International Patent Classification⁷: B29C 35/02, 39/02, 67/04, B29K 1/00, 29/00, 67/00, 77/00, 305/00, 309/02, 505/02, 509/02, A61K 9/52, 9/58, 9/60, 47/30, 47/36, 47/38

Street, Parkville, VIC 3010 (AU). UNIVERSITY OF NEWCASTLE [AU/AU]; University Drive, Callaghan, NSW 2308 (AU).

(21) International Application Number: PCT/AU01/00395

(22) International Filing Date: 6 April 2001 (06.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PQ 6772 7 April 2000 (07.04.2000) AU

(71) Applicants (*for all designated States except US*): ALBRIGHT AND WILSON (AUSTRALIA) LIMITED [AU/AU]; ACN 004 234 137, 295 Whitehall Street, Yarraville, VIC 3013 (AU). FOOD SCIENCE AUSTRALIA [AU/AU]; Sneydes Road, Werribee, VIC 3030 (AU). THE UNIVERSITY OF MELBOURNE [AU/AU]; Grattan

(72) Inventors; and

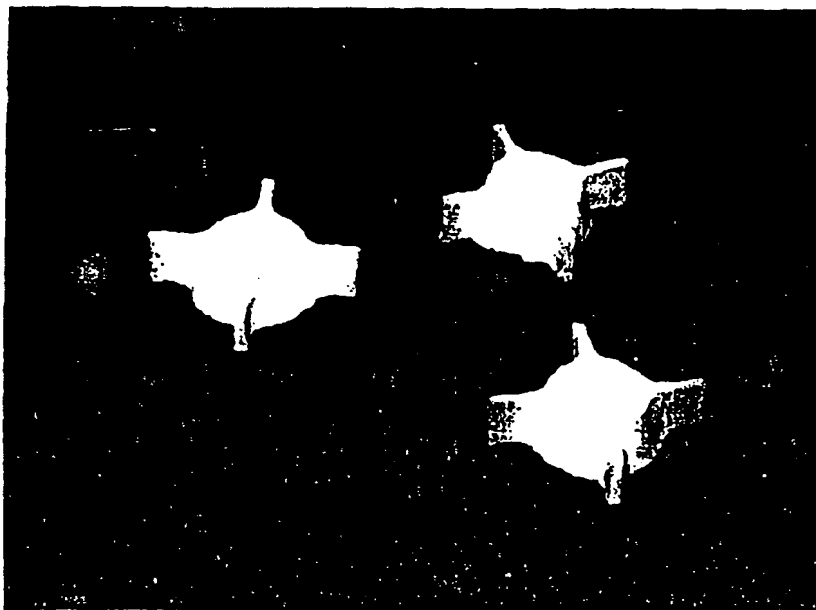
(75) Inventors/Applicants (*for US only*): FRANKS, George, Vincent [US/AU]; 30 Railway Street, Dudley, NSW 2290 (AU). JOHNSON, Stephen, Bruce [AU/AU]; 174 Moore Street, Fitzroy, VIC 3065 (AU). DUNSTAN, David, Edwin [AU/AU]; 22 Wyuna Street, West Brunswick, VIC 3056 (AU).

(74) Agents: ROBERTS, Mark, K. et al.; Davies Collison Cave, 1 Little Collins Street, Melbourne, VIC 3000 (AU).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

[Continued on next page]

(54) Title: METHODS OF FORMING SHAPED ARTICLES FROM SUSPENSIONS



(57) Abstract: The invention relates to methods of forming shaped articles from suspensions which include ceramic or metallic powder, or from solutions or suspensions which include one or more pharmaceutical substances or other components. The method comprises the steps of: (a) combining solvent, polymer, cross-linking agent precursor and optional further components and placing into a mould of desired shape; (b) increasing temperature of mould contents to activate cross-linking agent; (c) allowing mould contents to solidify to sufficient extent to remove mould; (d) removing shaped article from the mould.

BEST AVAILABLE COPY

WO 01/76845 A1

- 1 -

Methods of Forming Shaped Articles from Suspensions

FIELD OF THE INVENTION

- 5 The present invention relates to methods of forming shaped articles and in particular, but not exclusively, to methods of forming shaped articles from suspensions which include ceramic or metallic powder or from solutions or suspensions which include one or more pharmaceutical substances or other components. The shaped articles which include one or more pharmaceutical substances can be employed as pharmaceutical controlled release
10 formulations.

BACKGROUND OF THE INVENTION

- It is impractical to cast ceramics from the molten state as is commonly done with many
15 metal alloys. This is primarily due to the requirement of a highly refined defect free microstructure necessary to produce reliable components with properties for high performance applications. Furthermore the high melting temperature and/or decomposition of the material makes melting impossible or economically impractical.

- 20 High performance ceramic materials thus must be made from fine powders that sinter (densify) at a temperature below their melting point. The reduction in free surface energy is the driving force for the elimination of porosity and the densification.

- Ceramics are inherently brittle materials and are thus sensitive to flaws which reduce the
25 strength and reliability of the final article. The strength (S) depends on the fracture toughness of the material (K_{IC}) and the size of the flaw or crack (c) as follows:

$S = YK_{IC}/\sqrt{c}$. The fracture toughness is a material property and Y a geometric factor that depends upon the details of the flaw shape. Large flaws and cracks greatly reduce the strength of the material.

30

- 3 -

generally results in lengthy and costly heat treatments, cracking, distortion, and generally low quality components (German *et al.* 1991). Furthermore, many of these processes utilise equipment originally designed for plastics manufacture. The use of abrasive ceramic particles in these metal devices which are operated under high pressure, results in wear of the equipment and detrimental metallic inclusions in the article. Systems that utilise thermosetting binders such as epoxies (US patent No. 2,939,199, US patent No. 4,456,713, Takeshita *et al.* 1997) suffer from many of the same problems, particularly including lengthy and detrimental binder burnout processes.

Low pressure injection moulding (Mangels 1994) processes may alleviate at least the abrasion problem associated with the high pressure injection moulding processes, but by itself does not address the binder problems. The Quickset injection moulding process, (US patent No. 5,047,181, US patent No. 5,047,182) utilises a low pressure injection moulding (or pourable) process with only a few percent of a binder in either aqueous or non-aqueous solvents. This method utilises the freezing of the suspending medium as the method of changing the suspension behaviour from liquid-like to solid-like. This system has the advantage that the solidification can occur very quickly. The disadvantage of this system is that it requires a lengthy and costly (sublimative) freeze drying process since the parts would melt and lose shape if heated under atmospheric pressure during drying. The advantage of the above mentioned thermoplastic and low pressure injection moulding formulations is that temperature may be used as a switch mechanism for controlling the suspension behaviour as either a liquid-like or a solid-like material.

Recently another pourable or low pressure injection mouldable process which utilises an aqueous system has been disclosed (US patent No. 5,667,548, US patent No. 5,788,891, US patent No. 5,948,335, Balzer *et al.*, 1999). This method relies on a chemically activated change in solution conditions that change the particle-particle interaction from repulsive to attractive. This process requires particularly long retention times in the mould to achieve strength sufficient to successfully remove the mould. The published results indicate that it takes 24 hours for the articles to achieve a strength of about 8 kPa. (Balzer *et al.* 1999) With this system, once all the components are added to the suspension the gelation begins

- 5 -

pharmaceutical controlled release formulations and shaped articles containing other components. The present invention allows the encapsulation of pharmaceutical substances which can be released at a controlled rate following administration. The adoption of this technology in the preparation of pharmaceutical controlled release formulations has the advantage of allowing thorough mixing of the pharmaceutical substance within the gel forming mixture with the ability to readily manipulate gel strength and thus also the rate of pharmaceutical substance release.

It is with the above background in mind that the present invention has been conceived.

10

SUMMARY OF THE INVENTION

According to one embodiment of the present invention there is provided a method of forming a shaped article comprising the steps of:

- 15 (a) combining solvent, polymer, cross-linking agent precursor and optional further components and placing into a mould of desired shape;
- (b) increasing temperature of mould contents to activate cross-linking agent;
- (c) allowing mould contents to solidify to sufficient extent to remove mould;
- (d) removing shaped article from the mould.

20

In preferred embodiments of the invention the polymer may be selected from the group chitosan, polyvinylalcohol, chitin, polyacrylic acid, polyvinylacrylate, polyacrylate, polyacrylamide, pectin, xanthan gum, polymers having amide, amine, carboxylic acid and/or hydroxyl functionalities, and mixtures thereof.

25

Preferably the cross-linking agent precursor forms a multifunctional aldehyde upon temperature increase and particularly preferably the cross-linking agent precursor forms a di-aldehyde upon temperature increase.

- 30 In a preferred embodiment of the invention the cross-linking agent precursor is 2,5-dimethoxy-2,5-dihydrofuran (DHF).

Figure 1. The storage modulus of a 1.5 wt% chitosan / 2.5×10^{-2} mole dm^{-3} DHF solution at pH = 1.4 as a function of temperature and time. ● = 40°C; ○ = 50°C; ▲ = 60°C; △ = 70°C; ◆ = 80°C; ◇ = 90°C; ▼ = 98°C.

5

Figure 2. The storage modulus of a 1.5 wt% chitosan / 2.5×10^{-2} mole dm^{-3} DHF solution as a function of both time and several pH conditions. The temperature was 80°C. The pH was ● = 0.9; ○ = 1.4; ▲ = 2.1.; ◇ = 3.1; ◆ = 3.9.

10 Figure 3. The storage modulus of a 1.5 wt% chitosan solution at pH = 1.4 as a function of both DHF concentration and time. The temperature was 80°C. The DHF concentration was ● = 1.0×10^{-2} mole dm^{-3} ; ○ = 2.5×10^{-2} mole dm^{-3} ; ▲ = 5.0×10^{-2} mole dm^{-3} ; △ = 1.0×10^{-1} mole dm^{-3} .

15 Figure 4. Viscosity verses shear rate for a 45 v% AKP-30 alumina suspension in a 1.0 wt % (per solution weight) solution at 20 °C at pH ● = 1.1; ○ = 1.4; ▲ = 2.2.; ◇ = 3.2; ◆ = 4.5.

20 Figure 5. Shear modulus as a function of time for 45 V% alumina suspensions in 1.0 wt % chitosan solutions with 100 mM DHF at pH 2.2, at various temperatures. ●, 20°C; ○, 60°C; ▲, 80°C; △, 98°C.

25 Figure 6. Shear modulus as a function of time for a 45 v% AKP-30 alumina suspension in a 1.0 wt % (per solution weight) solution with 100 mM DHF at 80°C at pH ● = 1.1; ○ = 1.4; ▲ = 2.2.; △ = 3.2; ◆ = 4.5.

30 Figure 7. Shear modulus as a function of time for a 45 v% AKP-30 alumina suspension in a 1.0 wt % (per solution weight) solution at pH 2.2 at 80°C with various DHF concentrations ● = 20 mM; ○ = 50 mM; ▲ = 100 mM.; △ = 200 mM.

Figure 15. Effect of pH on the viscosity (at 25°C and 0.1 s⁻¹) of suspensions prior to gelation and the strength of the body after gelation. The suspensions contained 45 V% alumina, 1.0 wt % (by solution wt.) chitosan, 200 mM DHF, and were gelled at 85°C for 30 mins.

5

Figure 16. Effect of heat treatment time on the strength of wet gelled bodies. The suspensions contained 45 V% alumina, 1.0 wt % (by solution wt.) chitosan, 100 mM DHF, at pH 2.2 and were gelled at 85°C for the indicated times.

10

Figure 17. Stress-strain behaviour of cylinders made from suspensions containing 45 V% alumina, 1.0 wt % (by solution wt.) chitosan, 100 mM DHF, at pH 2.2 heat treated for 30 mins. at the indicated temperatures.

Figure 18. Shear modulus as a function of time for a 30 v% Zirconia suspension in a 1.0 wt % chitosan solutions with 80mM DHF at pH 2.2 at various temperatures ● 20°C , ○ 60°C, ▲ 80°C, Δ 98°C

Figure 19. Shear modulus as a function of time for a 30 v% Zirconia suspension in a 1.0 wt % (per solution weight) solution at pH 2.2 at 80°C with various DHF concentrations ● = 20 mM, ○ = 50 mM, ▲ = 80 mM, Δ = 100 mM

20

Figure 20. Shear modulus as a function of time for a 45 v% Silicon nitride suspension in a 1.0 wt % chitosan solutions with 80mM DHF at pH 2.0 at various temperatures ● 20°C, ○ 60°C, ▲ 80°C, Δ 98°C.

25

Figure 21. Shear modulus as a function of time for a 45 v% Silicon nitride suspension in a 1.0 wt % (per solution weight) solution at pH 2.0 at 80°C with various DHF concentrations ● = 20 mM, ○ = 50 mM, ▲ = 80 mM

The key components of the shaped articles produced according to the present invention are a solvent, a polymer and a cross-linking agent precursor. These basic constituents may have further optional components added to them depending upon the nature of the shaped article to be produced. For example, in the case of production of ceramic or metallic articles, ceramic or metallic powders such as alumina, zirconia, silica, silicon nitride, silicon carbide, aluminium nitride, ceramic superconductors and mixtures of these may be included within the solvent, polymer and cross-linking agent precursor mixture to form a suspension. Cross-linking of the polymer will form a gel, under controlled conditions, which can support the particles within their desired shape before sintering is undertaken.

Similarly, in the case of foodstuffs or pharmaceutical formulations, food material components such as proteins, carbohydrates, fats and/or nucleic acids which may of course be in combination, or in the case of pharmaceutical agents or nutritional supplements, vitamins, minerals or therapeutically active agents may be included. The present invention also extends to the preparation of shaped articles which may include other biologically active agents such as herbicides, pesticides, fungicides, parasitocides, antifungal agents or antiviral agents, which are mentioned by way of example only. Such articles may, for example, be utilised to allow controlled release of agrochemicals. In some contexts it may be desired for dispersants, chelating agents, surfactants, salts, colouring agents or flavouring agents to be incorporated within the combined solvent, polymer and cross-linking agent precursor material, optionally with further components as referred to above. In the context of pharmaceutical formulations, pharmaceutically acceptable carriers and/or additives as for example disclosed in Remington's Pharmaceutical Sciences, 18th Edition, 1990, Mack Publishing Co, Easton, Pennsylvania, USA (as included herein in its entirety by way of reference) may also be included.

By way of example, the pharmaceutical agents according to the invention may include gastrointestinal agents, electrolytes and haematologic agents, cardiovascular agents, respiratory acting agents, neuroactive agents, hormones, vitamins and nutrients, enzymes, anaesthetics, sedatives, hypnotics, anti-epileptics, muscle relaxants, analgesics, antipyretics, antihistamines, parasitocides, antimicrobial agents, antibiotics, immunising agents and the like. Specific examples of these classes of pharmaceutical agent are

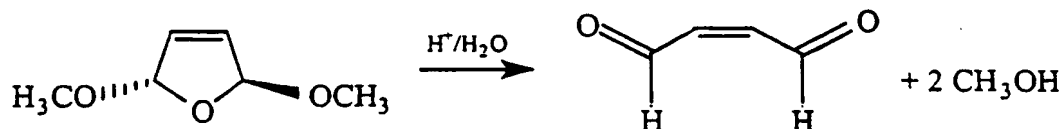
- 13 -

The cross-linking agent precursors which may be adopted in the present invention are those which can be activated by an increase in temperature to form a cross-linking agent effective to cross-link the particular polymer or polymer mixture concerned. Preferred cross-linking agents according to the invention include ring opening molecules, and in particular the cross-linking agent precursors may be those that form a multifunctional aldehyde upon increase in temperature. Preferably the multifunctional aldehyde is a di-aldehyde which is formed from the cross-linking agent precursor when it is exposed to increased temperature.

- 10 A particularly preferred cross-linking agent precursor is 2,5-dimethoxy-2,5-dihydrofuran (DHF).

When present in acidified aqueous solution, 2,5-dimethoxy-2,5-dihydrofuran (DHF) decomposes to yield butenedial according to the scheme (Hansen, et al., 1997):

15



Other cross-linking agent precursors which may be adopted include any molecule which degrades with increase in temperature to produce butenedial.

20

Solutions of chitosan or other polymers are used as the continuous liquid phase in which the ceramic or metal powder may be dispersed. Usually between 0.1 and 8 wt % of polymer is used relative to weight of ceramic or metallic powder. Similar concentrations are typical if the polymer concentration is based on solution weight. The concentration of ceramic or metal powder in the mixture will depend on the particle characteristics, but particle concentrations near the maximum packing are usually preferred. The concentration of powder in the mixtures is typically between 20 and 75 volume percent. A relatively low viscosity (although sometimes shear thinning) suspension is produced so that the suspension may be poured or injected into the mould. Figure 4 shows the viscosity

concentration of the cross-linking agent. Generally increasing the cross-linker concentration will increase the rate of gelation and the stiffness of the gelled body formed (See Figures 7 and 8).

- 5 The slight shear thinning behaviour observed in Figure 4 is due to Al^{3+} ions in the solution (dissolved from the alumina particles at low pH) forming weak links between chitosan molecules. The viscosity of the suspension at room temperature (before gelation) may be further reduced by the addition of a chelating agent that binds Al^{3+} ions preventing them from weakly cross-linking the chitosan. Anions such as F^- and citrate have been found to
10 be effective in this role. It should be noted that even if no chelating agent is used the links created with polyvalent ions are only weak and reversible, thus not creating a significant problem.

After preparation of a suitable suspension, solution or dispersion (as described above and
15 as referred to in the examples below) a complex shaped article can be fabricated by transferring the suspension into a porous or non-porous mould and activating the cross-linking agent. The suspension may be transferred to the mould by pouring, vibratory filling or pressurised (low or high) injection. The mould may be an open or closed cavity mould. The mould material may be plaster, metal, ceramic or polymeric. Generally a
20 closed cavity stiff mould with high thermal conductivity is preferred. These properties allow for quick heat transfer and good dimensional control. A closed non-porous mould prevents any drying of the body during gelation which may in some cases give rise to unwanted defects. Injecting the suspension into the mould under relatively low pressures facilitates complete filling of the mould and good dimensional control.

25

Heat treating the mould containing the suspension at elevated temperature causes the cross-linking agent precursor to form the active cross-linking agent which initiates the gelation. DHF and other temperature activated ring opening molecules are particularly advantageous since in the closed ring form they do not cross-link the polymer and the
30 suspension viscosity remains low for extended periods of time, while in the opened form (at higher temperature) these molecules quickly form cross-links resulting in rapid

- 17 -

After removal from the mould the body may be dried and fired in accordance with the methods typically used by those well skilled in the art. Difficult or costly drying or binder burnout steps are usually not required to produce high density, strong, uniform and reliable ceramic or metallic components with well controlled dimensions. With this method net shape and near net shape high performance ceramic and metallic components can be manufactured, although if necessary in particular applications some machining of the article may be required.

When the shaped articles take the form of pharmaceutical formulations they may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or may be enclosed in hard or soft shell gelatine capsule, or may be in the form of tablets. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, pills, buccal tablets, troches, lozenges, wafers, and the like. Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations may of course be varied and may conventionally be between about 5 to about 80% of the weight of the shaped article. The amount of active compound(s) in the pharmaceutical compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 0.5 ng and 320 mg of active compound.

The tablets, troches, pills capsules and the like may also contain the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate, a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavouring agent such as peppermint, oil of wintergreen, or cherry flavouring. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed.

(3) The rate of gelation and magnitude of the maximum shear modulus increase as a function of rising DHF concentration. Such results are consistent with an increase in the rate of DHF conversion into butenedial, leading to a corresponding increase in the rate and extent of gelation. (See Figure 3.)

5

Example 2

Change in Rheological Behaviour of Suspension During Gelation

A high purity α -alumina powder (AKP-30) was obtained from Sumitomo Corporation (Japan). It possessed a BET surface area of $7 \text{ m}^2 \text{ g}^{-1}$, a mean particle diameter of $0.3 \mu\text{m}$ and a density of 3.97 g cm^{-3} . A high molecular weight chitosan was purchased from Fluka BioChimika (Switzerland). It had a molecular weight of 2×10^6 and a degree of de-acetylation (DD) of approximately 87 per cent (Berthold, *et al.* 1996). The DD is an indicator of the proportion of hydrophilic (de-acylated) amine groups to hydrophobic acetamide moieties on the chitosan chains, with a high DD favouring good aqueous solubility to form low viscosity solutions. Cis / trans 2,5-dimethoxy-2,5-dihydrofuran (DHF) was obtained from Tokyo Kasei. The pH of all solutions and suspensions was adjusted using analytical grade hydrochloric acid and sodium hydroxide (both from Ajax Chemicals, Australia). All water used in this study was of Milli-Q grade (conductivity $\approx 10^{-6} \text{ S m}^{-1}$ at 20°C).

Aqueous alumina suspensions with solids concentrations of 59 vol% were prepared by ultrasonication under acidic conditions using a Branson 450 sonifier equipped with a 0.75 inch horn. The sonifier was operated at a frequency of 20 KHz, with the power output maintained at approximately 90 per cent of the limiting power (350 W). The samples were then slowly tumble-mixed for several hours prior to use.

Example 3

Formation of Complex Shaped Articles

5 A suspension containing 45 vol% alumina, a solution chitosan concentration of 1.0 wt%, as described in Example 2. The viscosity of the suspension was measured using the 'Viscometry' function of the Stresstech rheometer, again in a cone-and-plate geometry as in Example 2. As all viscometry measurements were performed at 20 °C, evaporation was not found to affect the results obtained over the experimental time-frame. The use of silicone oil was therefore not deemed to be necessary. Figure 4 is a plot of viscosity verses
10 shear rate for suspensions at 20 °C at various pH values from 1.1 to 4.5. This figure indicates that at room temperature the suspension is slightly shear thinning but the viscosity is relatively low. The behaviour of the suspension is liquid-like and it is pourable and injectable.

15 One hundred millimole dm^{-3} (mM) DHF was added to the suspension. The suspension was allowed to mix for between 2 and 8 hours. The addition of the DHF and mixing did not significantly affect the rheological behaviour of the suspension.

20 A small die cavity (outside diameter 6.35 cm and 2.30 cm tall) was designed and fabricated out of aluminium to produce a pseudo-rotor that incorporated both varying cross section, and vane-like protrusions to demonstrate the process capability. The pseudo-rotor mould cavity outside diameter (including vanes) is 3.70 cm and its height is 1.10 cm. A second, simple cylindrical mould was fabricated so cylinders could be formed to be tested for determination of the mechanical properties of the gelled bodies. The dimensions of the
25 cylindrical cavity was 2.40 cm in diameter and 1.10 cm in thickness. A 50/50 mixture of WD-40 and silicone grease was used as a mould release agent. Only a light coating was applied.

The suspension was de-aired for 2 minutes using a siphon mechanism attached to a tap.
30 Some small bubbles (between 0.5 and 2 mm) were observed to rise to the suspension surface and break. The suspension was then poured into the mould cavity and tapped by

polymer, cross-linking agent and particles as well as the gelation conditions such as time and temperature must be carefully controlled. The components had good surface quality replicating the shape and texture of the mould well.

- 5 The bodies were dried in air for between 16 and 36 hours and further dried at 110°C for two hours. The total shrinkage of the parts during gelation (due to syneresis) and drying was measured to be between 5.0 and 5.5 %. The weight of the parts before and after drying and the density of alumina and water were used to calculate the green density of the gelled bodies. These measurements confirmed the green density of the gelled parts was
- 10 45 V% as the suspension was formulated. The dried pseudo rotors were fired at 1450°C for two hours in a Blue M furnace in air. Figure 9 is a photo of the fired parts. The parts had densities ranging from 3.73 to 3.84 g/cc, corresponding to between 94 and 97% of theoretical density (see Table I). The final dimensions of the fired pseudo rotors were, 2.95 cm outer vane diameter and 0.85 cm tall. These dimensions corresponding to a total
- 15 shrinkage of between 20 and 21% based on the mould dimensions.

Example 4

Strength of Wet (Saturated) and Dried Gelled Bodies

- 20 The mechanical behaviour of the bodies produced with this invention were measured utilising an Instron Dynamight 8841 test frame with a 1kN load cell. The cylindrical specimens produced in Example 3 above were tested in diametral compression. This testing configuration produces a maximum tensile stress in the centre of the cylinder acting perpendicular to the axis of the loading and parallel to the plane in which the cylinder flat
- 25 surfaces lie. With this method a tensile fracture strength of bodies can be measured without producing complex shaped tensile specimens.

- Specifically Cylinders # 1 and #2 were dried as described in Example 3 at room temperature for about 24 hours and at 110 °C for 2 hours. The specimens were allowed to
- 30 cool to room temperature before testing. Cylinders # 3 and # 4 were tested immediately (within 1 minute) of removal from the mould. Cylinders #3 and # 4 were still saturated

- 25 -

Cylinders were formed from the suspensions following the procedure described in Example 3. The mechanical behaviour of the saturated cylinders was measured with an Instron Dynamite 8841 test frame in the diametral compression configuration as described in Example 4. The typical stress-strain behaviour of the saturated gelled bodies is shown in Figure 14. The bodies exhibit significant strain to failure ratio characteristics with behaviour that is similar to a jelly (coloured, flavoured, gelatine food product). Deformation resulted in initially elastic deformation followed by plastic deformation until fracture occurred. It was not possible to distinguish between the linear and nonlinear elastic deformation or when the plastic deformation began. The large elastic flexibility of the bodies before failure give the body a resistance to fracture that is helpful in removing the body from the mould. The fracture strength increases from 50 mM to about 100 mM then tends to level off as indicated in Figures 13 and 14. Correspondingly, the strain to failure ratio is greatest for the 50 mM containing body but decreased and about the same for the bodies containing between 100 and 200 mM DHF. These changes in mechanical behaviour appear to be due to the greater amount of crosslinking of the biopolymer with higher concentrations of DHF. A greater degree of polymer gel crosslinking produces a stiffer gel (higher elastic modulus) and a stronger polymer network. Figure 13 indicates that the preferred crosslinker concentration is 100 mM since this concentration produces viscosities near the minimum achievable with this chemistry, while producing gelled bodies with nearly the maximum strength attainable.

Example 6

Effect of pH

The pH of the suspensions has a complex effect on the chemical interactions between the alumina particles, chitosan and DHF (Mather et al., 1990). As pH is decreased both alumina and chitosan become increasingly positively charged. As the charge on chitosan increases its solubility increases. At pH above about 5.5 or 6 chitosan is not soluble because it has very little charge. At elevated temperature DHF decomposes to produce butenedial which is the active crosslinking agent. Both a high concentration of H^+ (low

Example 7

Effect of Time of Heat Treatment

Based on the initial rheological measurements of the alumina/chitosan/DHF system (see
5 Figures 5 through 8) it was believed that increased periods of gelation up to about 5 hours
would only produce stronger bodies. Surprisingly as shown in Figure 16, the greatest
strength bodies were produced after only 15 minutes of gelation. Shorter times were
insufficient for enough crosslinking to occur to produce solid like bodies. Longer times
produced gelled bodies that were slightly discoloured. The alumina suspensions are bright
10 white, as were the bodies produced after 15 minutes heat treatment. Bodies produced with
longer heat treatment times were slightly tan in colour. The tan colour becoming darker
with longer heat treatment times. Such behaviour is most likely due to the thermal
degradation of chitosan, which weakens the network strength of the parts. Another factor
that might contribute to the drop in strength of the bodies is syneresis. Syneresis is the
15 contraction of the gel and the squeezing out of free water bound from within the gel
structure. This phenomenon was observed in the samples with heating periods greater than
10 minutes, which indicates the presence of highly crosslinked networks. Naturally, with
an increased number of crosslinks, the gelled bodies become stiffer and less deformable.
These strongly gelled systems are highly susceptible to fractures leading to an apparent
20 decrease in strength.

Example 8

Effect of Temperature of Heat Treatment

25 The decomposition rate of DHF into butenedial is strongly dependent upon temperature
(Hansen et al. 1997). Since butenedial is the active molecule in chitosan crosslinking
process, an increase in the rate of DHF decomposition will lead to an increase in the level
of butenedial molecules and consequently, formation of stronger gelled bodies.
Cylindrical bodies were produced and mechanically tested as described in example 5. In
30 all cases the bodies were cooled to room temperature before de-moulding and mechanical
testing. At heat treatment temperatures below 65°C, the wet gelled bodies were sticky and

- 29 -

Small amplitude dynamic oscillatory measurements were performed in a cone-plate geometry using the 'Oscillation function' of the Carri-med Constant Stress Rheometer with a 4 cm, 1 59° cone. Evaporation was prevented by sealing the Zirconia/chitosan/DHF sample with a layer of paraffin oil.

5

The results of such rheological measurements are presented in Figure 18 for suspensions at pH 2.2 with 80 mM concentration of DHF measured at various temperatures between 20 and 98°C. This figure illustrates that at room temperature, the suspension does not gel and that increasing the temperature increases the rate of gelation and the final shear modulus of the suspension. Figure 19, demonstrates that the shear modulus and rate of gelation increased with concentration of DHF.

10

Example 10

Silicon Nitride Suspension

15

Silicon nitride powder (SN-E03) was obtained from UBE INDUSTRIES LTD (Japan). It possessed a surface area of 3.2 m²/g. A high molecular weight chitosan was obtained from Fluka Biochimika (Switzerland). It has a molecular weight of 2 x 10⁶. Cis/trans 2,5-dimethoxy-2,5-dihydrofuran (DHF) was obtained from Tokyo Kasei. The pH of all solutions and suspensions was adjusted using analytical grade hydrochloric acid and sodium hydroxide. All water used in this study was of triple distilled grade.

20

Chitosan stock solution was made at 2.0 weight %, in triple distilled water. The chitosan powder was mixed into water, with an overhead mixer, while the pH of the solution was constantly adjusted to 2.0, with appropriate volume of aqueous HCl. The solutions were used within 24 hours of preparation.

25

REFERENCES

- Balzer, B., Hruschka, M. K. M., and Gauckler, L. J., *J. Colloid and Interface Sci.*, 216, 379-386 (1999).
- 5
- Berthold, A., Cremer, K., and Kreuter, J., "Preparation and Characterization of Chitosan Microspheres as Drug Carrier for Prednisolone Sodium Phosphate as Model for Anti-Inflammatory Drugs." *J. Control. Rel.*, 39, 17-25, (1996).
- 10
- Chen, Y., Xie, ZZZ. Yang, J., and Huang, Y., *J. European Ceramic Soc.*, 19, 271-275 (1999).
- German, R. M., Hens, K. F. and Lin, S.-T. P., "Key Issues in Powder Injection Moulding", *Am. Ceram. Soc. Bulletin*, 70 [8] 1294-1302 (1991)
- 15
- Hansen, E. W.; Holm, K. H.; Jahr, D. M.; Olafsen, K.; Stori, A., *Polymer*, 38, 4863-4871 (1997).
- Lange, F. F., "Powder Processing Science and Technology for Increased Reliability", *J. Am. Ceram. Soc.*, 72 [1] 3-15 (1989).
- 20
- Mangels, J. A., "Low Pressure Injection Moulding", *Am. Ceram. Soc. Bull.*, 73, 37-41 (1994).
- 25
- Mathur, N. K.; Narang, C. K. *J. Chem. Edu.* 67, 938-942 (1990)
- Pujari, V. K., Tracey, D. M., Foley, M. R., Paille, N. I., Pelletier, P. J., Sales, L. C., Willkens, C. A. and Yeckley, R. L., "Reliable Ceramics for Advanced Heat Engines", *Am. Ceram. Soc. Bulletin*, 74 [4] 86-90 (1995).
- 30

CLAIMS:

1. A method of forming a shaped article comprising the steps of:
 - (a) combining solvent, polymer, cross-linking agent precursor and optional
5 further components and placing into a mould of desired shape;
 - (b) increasing temperature of mould contents to activate cross-linking agent;
 - (c) allowing mould contents to solidify to sufficient extent to remove mould;
 - (d) removing shaped article from the mould.
- 10 2. The method according to claim 1 wherein the polymer is selected from the group chitosan, polyvinylalcohol, chitin, polyacrylic acid, polyvinylacrylate, polyacrylate, polyacrylamide, pectin, xanthan gum, polymers having amide, carboxylic acid and/or hydroxyl functionalities, and mixtures thereof.
- 15 3. The method according to either claim 1 or claim 2 wherein the cross-linking agent precursor forms a multifunctional aldehyde upon temperature increase.
4. The method according to either claim 1 or claim 2 wherein the cross-linking agent precursor forms a di-aldehyde upon temperature increase.
- 20 5. The method according to either claim 1 or claim 2 wherein the cross-linking agent precursor is 2,5-dimethoxy-2,5-dihydrofuran (DHF).
6. The method according to any one of claims 1 to 5 wherein the mould is filled by
25 pouring or by injection.
7. The method according to any one of claims 1 to 6 wherein the solvent is selected from water, ethanol, methanol, iso-propanol and mixtures thereof.
- 30 8. The method according to any one of claims 1 to 7 wherein the optional further components include ceramic or metallic powders.

1/21

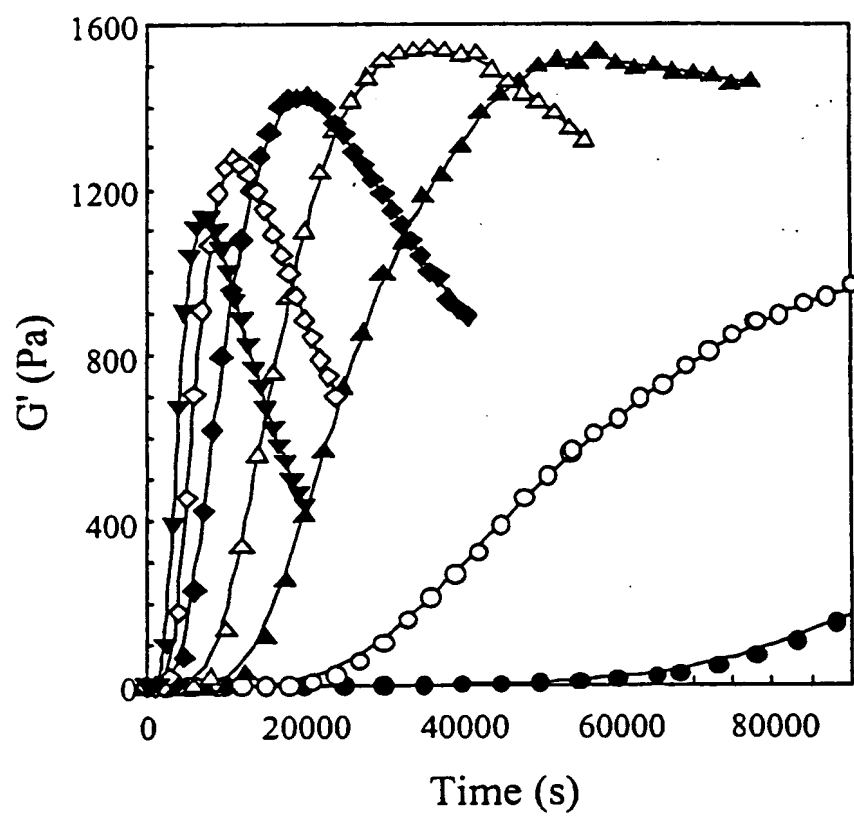


Figure 1

3/21

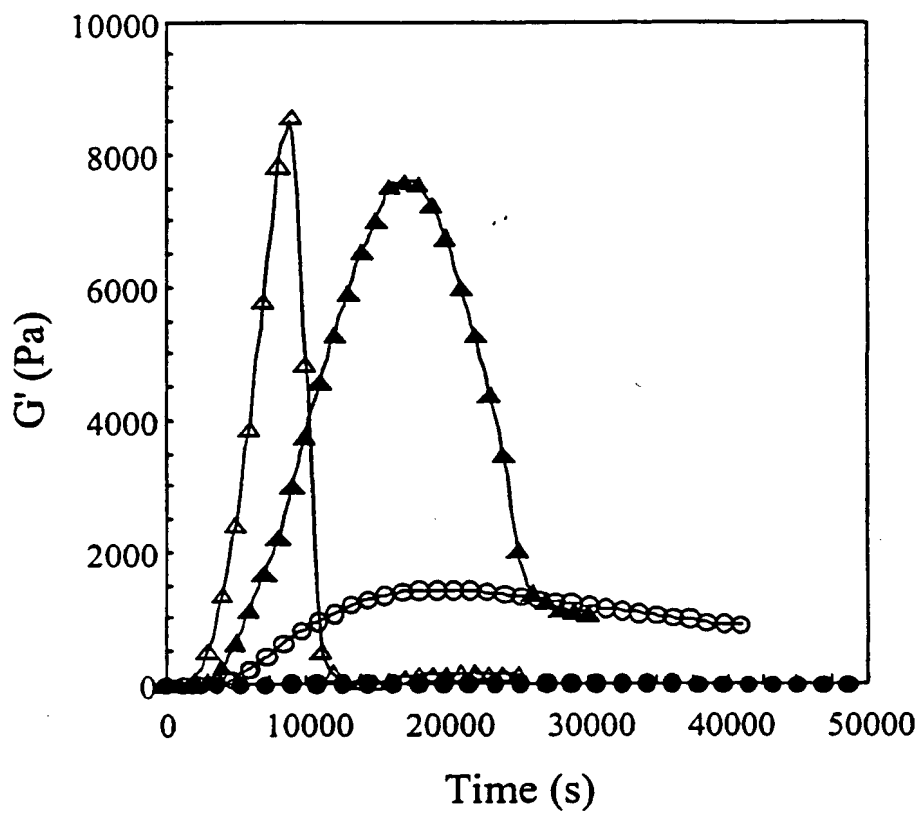


Figure 3

5/21

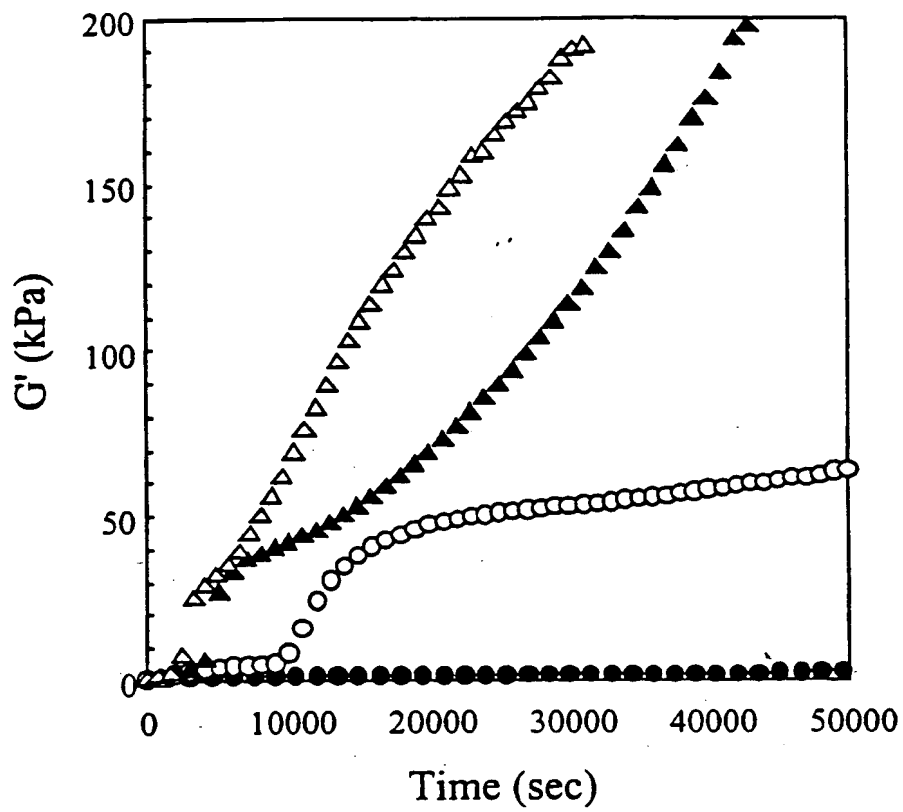


Figure 5

7/21

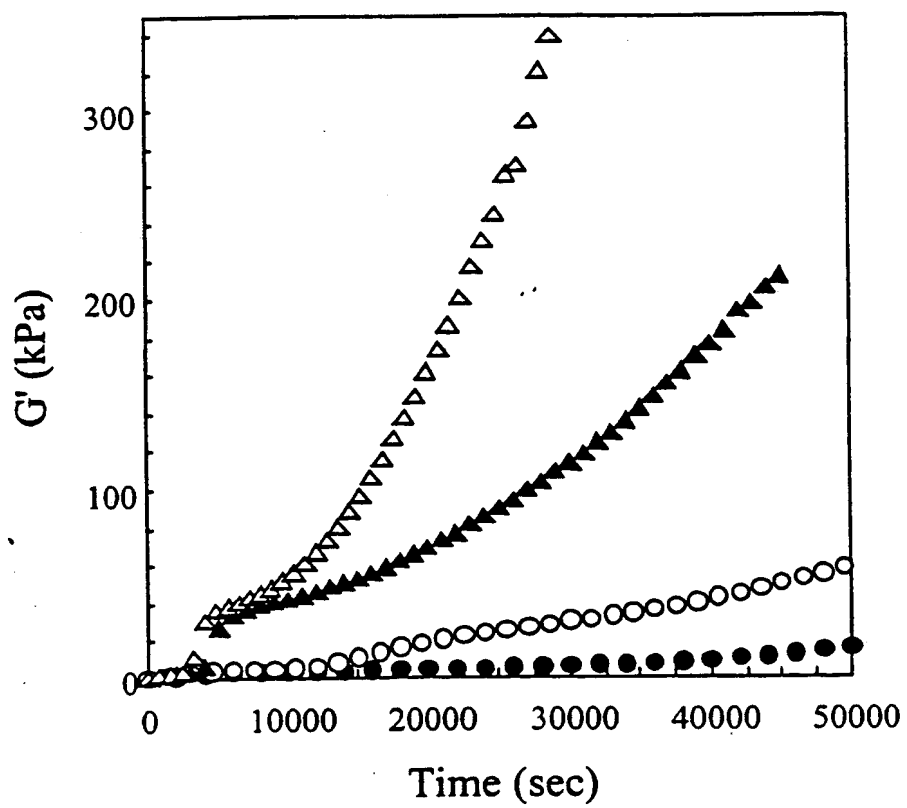


Figure 7

9/21

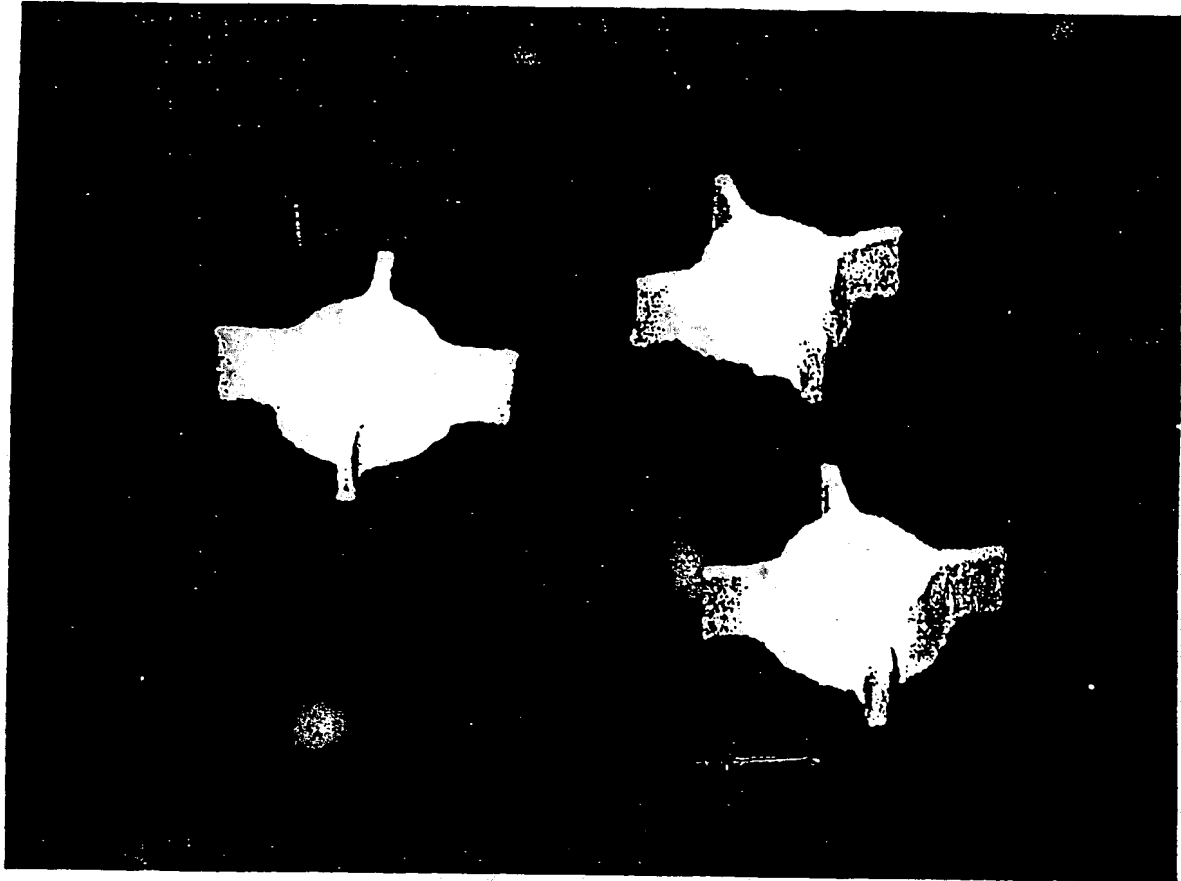


Figure 9

11/21

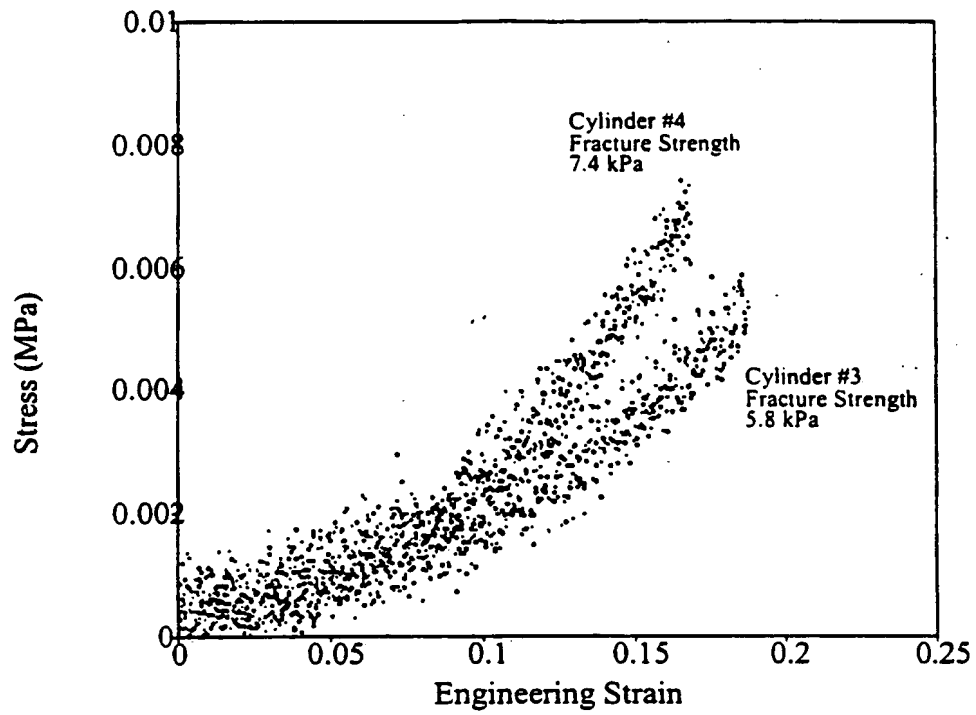


Figure 11

13/21

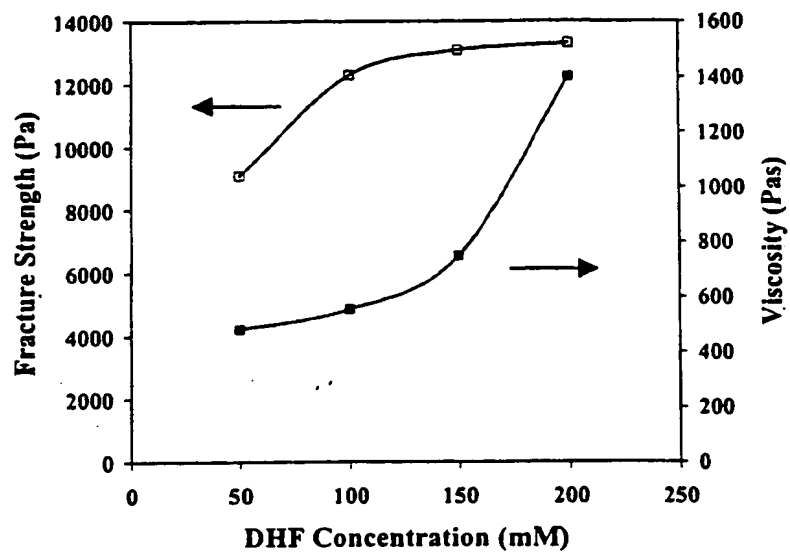


Figure 13

15/21

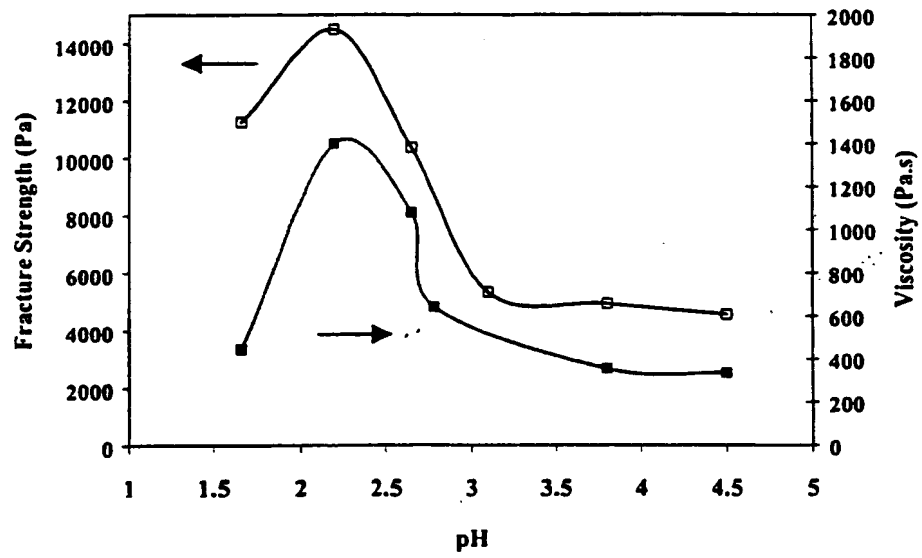


Figure 15

17/21

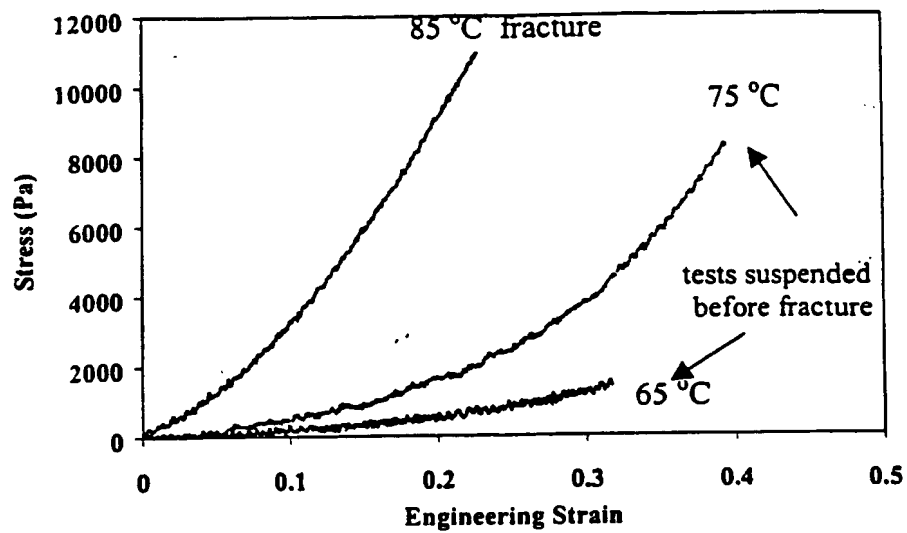


Figure 17

19/21

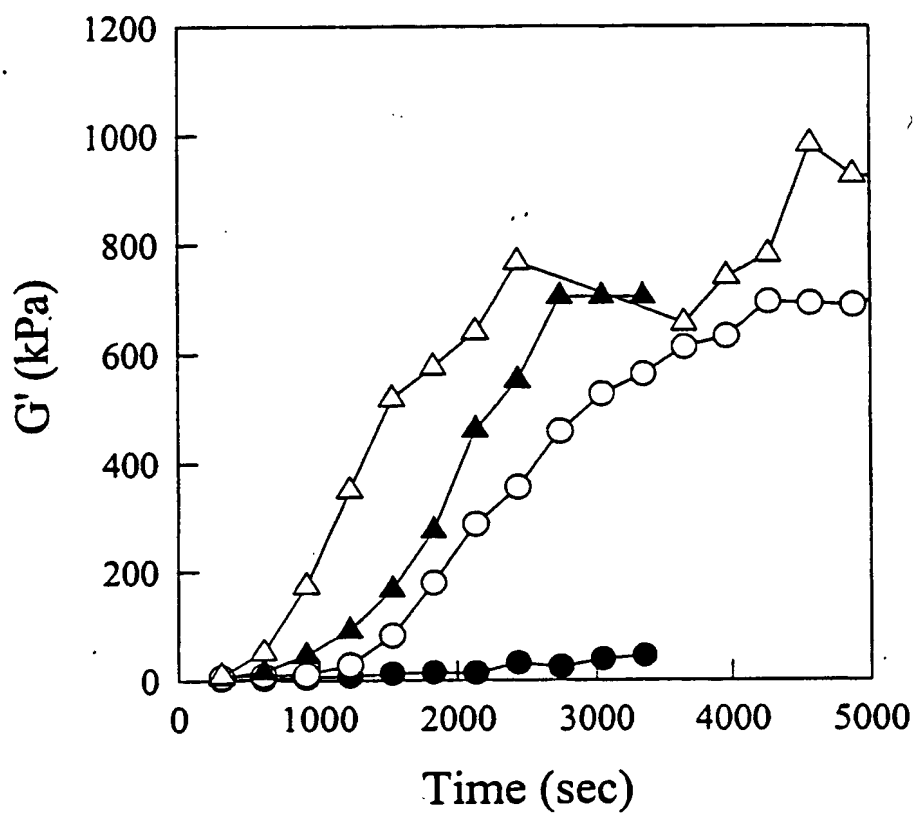


Figure 19

21/21

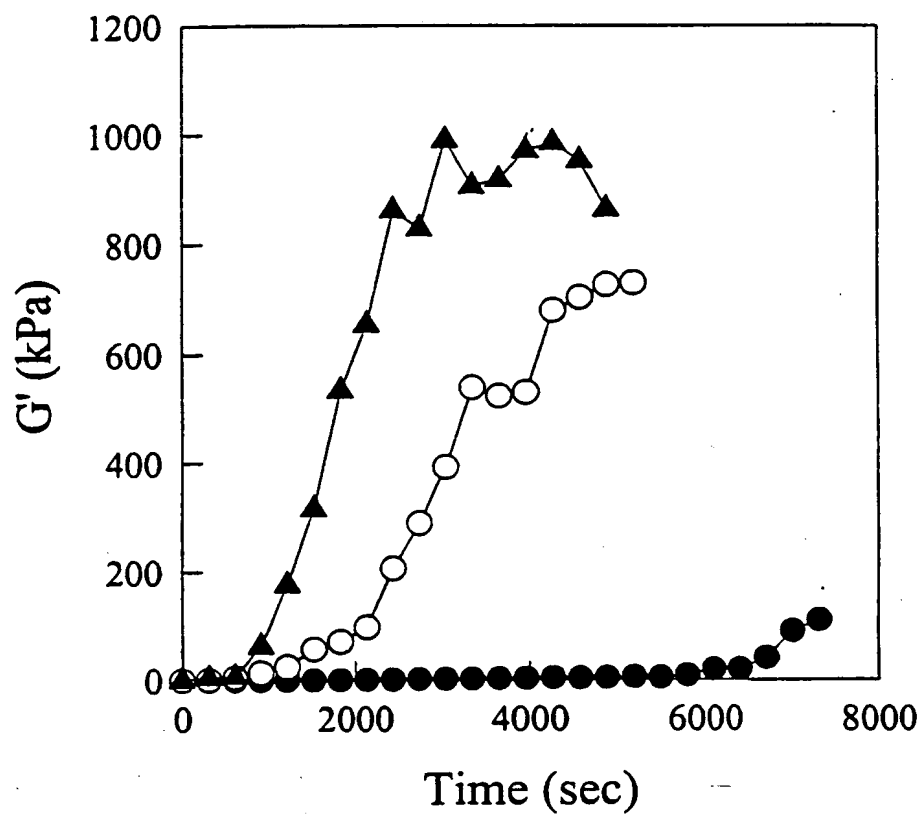


Figure 21

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU01/00395

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
WO 9624077	AU	45387/96	BR	9606942	CA 2211393
	CN	1173228	EP	807269	FI 973155
	IL	116901	NO	973512	NZ 300602
	US	6011077	ZA	9600826	
WO 9959804	AU	36943/99			
END OF ANNEX					

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.